THE SALK INSTITUTE

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Letter 1

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Dear Aaron,

I'm sorry for the delay in replying to your many interesting letters but I had a cold last week which made me rather thick-headed. Also I feel baffled by what you have told me. Naturally it would be easier seeing the e/m pictures but I think there is little point in sending me these as one really needs to brood over so many of them.

My main reaction is that you are trying to extract too much information from a very confusing mass of soft evidence. I feel the potential advantage of the x-ray single crystal approach is that it can lead to hard conclusions. Let me give an example. It seems to me very reasonable, from all the lines of evidence, to believe that the packing in the xy plane is the hexagonal packing of roughly "circular" objects. This leads naturally to the question, what is the "size" of the object in the z direction. Now if your density measurement, giving 12 nucleosomes per cell, is correct, then this distance must be of the order of 340/6 = 57 Å if the object is fairly compact. What one wants to know is whether this value for the clipped core particle fits the x-ray scattering and neutron scattering in solution and also the sedimentation value (the Stokes radius). Have all these measurements been made on the core particle, clipped or otherwise, and what are the results? From your letters and enclosures I gather that some of these have been done. Let me say that I don't think the work on either the tetramer or octamer without DNA helps a lot because of the problem of the "tails". So, as I see it, what one wants is a hard value for the density of the crystals and without this the arguments are only suggestive. However such a model does support the strong 006 and the general appearance of the b projection though one could easily argue that this could be deceptive.

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I agree that it may be possible, with luck, to guess the arrangement of the DNA in the nucleosome but how will one prove it? Everybody is now having a guess. If the x-ray phases were determined, however, the guessing would have to stop. Do I gather that you dispair of ever getting a rough idea of the phases by isomorphous replacement? I can see that the e/m plus the x-rays may perhaps suggest the broad arrangement of the nucleosomes in the cell but I doubt very much if you could find how the DNA folds this way. This is mainly because we lack any strong theoretical assumption to decide between alternatives (one such might be: DNA doesn't kink, it only bends).

However, there is one general argument you may be able to use. I am assuming that with 200 base-pairs per nucleosome there are about two turns of DNA, not one. (But see the enclosed correspondence with Walter Keller.) Then if you are going to make any sort of 250-300 Å solenoid you must have close DNA packing (say 25-30 Å) on the inner surface of the solenoid. There simply isn't space for wide (i.e. 40 to 50 Å) packing there. Thus the nucleosome must be fairly thin on one side. Whether, starting from this, you can deduce the rest of the shape, I rather doubt, though your wedge shape is a very plausible one.

I think I won't make any further detailed comments at this stage, as I need time to brood on the problem. Let me just deal with others points in your letters. About the four-stranded DNA. I have just written to the authors asking if they have a preprint. I don't think our efforts at four-stranded structure were worth anything and I've quite forgotten the argument about C's on one chain. The point of Morgan and Johnson's structure is that while one base-pair of the quadruple is standard, the other one is very non-standard and that not at all like McGavin's or Chen's.

I have now had an Mss from Abe Worcel. The idea is clear enough in a broad way but hopelessly badly expressed from our point of view. I assume you also have some sort of manuscript from him. If not, send me a telex and I will post you a xerox copy. I shall have to write to him about it shortly.

About the New Zealand SBS model. It looks too ugly to be true and your comments on their x-ray methods are very much to the point. If it were really side-by-side it would be easy to disprove but they've given it a small rotation of 36° or so per 10 base-pairs which makes it a little more difficult to refute. I doubt if it can be ignored completely. I have plans in my head to write a short note about it, perhaps for PNAS. If I do find the time to write a draft before I leave here on May 22 I'll show it you at Cold Spring Harbor.

I don't share your enthusiasm for the H4 fibers but perhaps I'm being too stuffy.

Incidentally I do feel, quite strongly, that there is a good case for preparing "Zachau" (DNA + the 4 histones) material and looking at fibers of that. He reports a repeat about 150 bp but my belief is that if they were made very carefully you might get a repeat nearer 140 bp and that micrococcal DNase might hardly touch it. (Remember Len's resistant dimers.) Moreover, as with Len's material, you should get very long 10 base ladders with DNase I. Perhaps fungal DNA has such material naturally -- I believe some was quite resistant to the enzyme -- in reasonable quantities.

Such fibers might give a very revealing x-ray pattern, especially if you get a good fiber diagram. I feel such an effort would be more worthwhile than much of the other non-crystal x-ray work. It really might decide how the DNA folds on the core nucleosome. This is because adjacent nucleosomes must have their DNA continuous with the next one, which is not necessarily true for the DNA in the core particles in the crystals.

While I remember it, exactly how much protein do you need to clip off a core particle to get the clipped particles which form 3-D crystals?

I have read the papers by Zachau and Chambon and have the general gist of them but I must reread them carefully. If I have any comments I'll send them to you. But first I must write to Joel about his paper, which I plan to do in the next couple of days. I also have a long explanatory letter from Michael Levitt which I will also reply to shortly. It's nice to have all these letters but I'm afraid they're not nearly as good as continual face-to-face discussion.

You ask if I am going to Spetsai. Sadly, I feel I ought not to do this as I have already cut my three month visit to Aarhus to six weeks, and that period includes a week at the FEBS meeting at Copenhagen and two or three days in Helsinki. However we shall at least be able to meet at CSH and at Copenhagen. Of course in the summer of 1978 I plan to spend 2 to 3 months at Cambridge but that seems a very long time away.

Apologies for this rather damp letter,

Yours ever,

Francis

F. H. C. Crick
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